PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P752PC00	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/DK2004/000492	International filing date *(day/month/year)* 08.07.2004	Priority date *(day/month/year)* 08.07.2003

International Patent Classification (IPC) or national classification and IPC
C07K16/12, C07K16/46, C12N15/13, C12N15/62, C12N5/10, G01N33/569, G01N33/577, A61K39/395, A61K39/40

Applicant
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1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 10 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 5 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04.05.2005	23.08.2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/DK2004/000492

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-72	as originally filed

Claims, Numbers

1-41	filed with telefax on 04.05.2005

Drawings, Sheets

1/19-19/19	as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1,2,5-7,10,11,17,19,24-41 (all partially)

because:

☒ the said international application, or the said claims Nos. 36 (partially, for reasons of industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1,2,5-7,10,11,17,19,24-41 (partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-41
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-41
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-35,37-41
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☒ furnished subsequently to this Authority for the purposes of search and/or examination

   ☒ received by this Authority as an amendment on

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item I

Basis of the report

The amendments filed with the letter dated 04.05.2005 do not introduce subject-matter which extends beyond the content of the application as filed, and hence fulfill the requirements of Article 34(2)(b) PCT.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Present claims **1, 2, 5-7, 10, 11, 17, 19** and **24-41** (all partially) relate to a product defined by reference to a desirable characteristic or property, namely an isolated binding member comprising at least one binding domain capable of specifically binding Streptococcus pneumoniae surface adhesin A (PsaA). The claims cover all products having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result. Consequently, a written opinion can only be given for the subject-matter that has been searched, i.e. that appeared to be clear, supported and disclosed, namely those parts relating to antibodies that specifically bind to Streptococcus pneumoniae surface adhesin A (PsaA).

Present claim **36** relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: J. SAMPSON ET AL.: 'Immunologic characterization of a monoclonal antibody to Streptococcus pneumoniae pneumococcal surface adhesin A (PsaA) protein.' ABSTRACTS OF THE GENERAL MEETING OF THE AMERICAN SOCIETY FOR MICROBIOLOGY, vol. 99, 1999, page 273, XP008027694, USA.

D2: H. RUSSELL ET AL.: 'Monoclonal antibody recognizing a species-specific protein from Streptococcus pneumoniae.' JOURNAL OF CLINICAL MICROBIOLOGY, vol. 28, no. 10, October 1990 (1990-10), pages 2191-2195, XP002109328, Washington, DC, USA.

D3: N. SRIVASTAVA ET AL.: 'Selection of an immunogenic and protective epitope of the PsaA protein of Streptococcus pneumoniae using a phage display library.' HYBRIDOMA, vol. 19, no. 1, February 2000 (2000-02), pages 23-32, XP001064205, New York, NY, USA.

D4: T. PILISHVILI ET AL.: 'Neutralization of attachment of Streptococcus pneumonia to human epithelial cells by recombinant PsaA and anti-PsaA antibodies.' ABSTRACTS OF THE GENERAL MEETING OF THE AMERICAN SOCIETY FOR MICROBIOLOGY, vol. 101, 2001, page 346, XP008027692, USA.

D5: WO 02 092017 A (L. PIROFSKY ET AL.) 21 November 2002 (2002-11-21)

1. NOVELTY (Article 33(2) PCT)

1.1 *D1* discloses mouse monoclonal antibody (mAb) Mab6F6 against PsaA which is reactive with all pneumococcal serotypes. Used for passive protection in vivo.

D2 discloses mouse mAb 1E7A3D7C2 recognizing a 37 kD species-specific protein from S. pneumoniae. Used for detection.

D3 discloses a.o. mouse mAbs 8G12, 6F6 and 1B7 specific for a peptide from PsaA. mAb 4E9 reacts with a peptide in the N-terminal half of the PsaA protein

D4 discloses a.o. neutralizing rabbit polyclonal antibodies against psaA. In vivo protection suggested.

D5 discloses human anti-pneumococcal mAbs specific for capsular polysaccharide PPS-3, their variable region's sequences, vectors, host cells. Also therapeutic use of said antibodies has been claimed.

1.2 None of the prior art documents discloses a (human) antibody specific for Streptococcus pneumoniae PsaA with a Kd < 5×10^{-9} M. Hence, present claims **1-41** appear to be novel and meet therefore the requirements of Article 33(2) PCT.

2. INVENTIVE STEP (Article 33(3) PCT)

2.1 The subject-matter of present independent claim **1** deals with an isolated binding member comprising at least one binding domain capable of specifically binding PsaA protein, said binding domain having a dissociation constant Kd for PsaA which is less than 5×10^{-9} M, such as less than 1×10^{-9} M. With regard to said claim **1**, *D3* is considered to represent the most relevant state of the art and discloses a.o. mouse mAbs 8G12, 6F6 and 1B7 specific for a peptide from PsaA. Present claim **1** differs from D3 in that the claimed isolated binding member has a Kd < 5×10^{-9} M for PsaA. The technical effect is an isolated binding member with a **high binding affinity** for PsaA.

The problem to be solved may therefore be regarded as providing an isolated binding member with a specified binding affinity for PsaA.

This problem has been solved by the present invention and involves an inventive step in the sense of Article 33(3) PCT: Such a high affinity for the PsaA antigen has not been disclosed or suggested before in the prior art for a PsaA-specific isolated binding member. Moreover, the underlying application discloses **human** mAbs against PsaA with said high affinity. No human mAbs against PsaA have been disclosed or suggested in the prior art, adding to the inventive step required to arrive to the present invention.

2.2 Consequently, also the subject-matter of those claims dependent on present claim **1**, i.e. present claims **2-30**, involve an inventive step in the sense of Article 33(3) PCT.

2.3 Since present independent claims **31, 32, 34, 35, 36, 37, 38, 40** and **41**, and claims dependent on them, all eventually refer back to the novel and inventive claims **1-30**, also claims **31-41** are considered to involve an inventive step in the sense of Article 33(3) PCT.

3. INDUSTRIAL APPLICATION (Article 33(4) PCT)

3.1 For the assessment of the present claim **36** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

4. CLARITY & SUPPORT (Article 6 PCT)

4.1 The term 'binding member' in present claims **1-31** and **35-41**, the term 'immunologically active fragments' in present claim **3**, and the term 'homologue' in present claims **12-16** and **18**, is vague and indefinite and renders the scope of said claims unclear in the sense of Article 6 PCT.

However, the following definitions would be considered as clear:
- Instead of the term 'binding member': 'a binding polypeptide', which finds its basis in page 10 (lines 17-18) of the description. Also the term 'antibody' would be clear.
- Instead of the term 'immunologically active fragments': 'antigen-binding fragments', which finds its basis in page 9, lines 16-26, and page 17, lines 17-20, of the description.

4.2 According to Article 6 PCT, the claims should be supported by the description. In the description, the only binding members that have been disclosed and support the claims are antibodies (see the examples).

Amended claims filed May 4, 2005.

1. An isolated binding member comprising at least one binding domain capable of specifically binding Streptococcus pneumoniae surface adhesin A (PsaA) protein, said binding domain having a dissociation constant K_d for PsaA which is less than 5×10^{-9} M, such as less than 1×10^{-9} M.

2. The isolated binding member according to claim 1, wherein the isolated binding member is a pure isolated binding member.

3. The isolated binding member according to claim 1, wherein the binding member is selected from antibodies or immunologically active fragments of antibodies or single chain of antibodies.

4. The isolated binding member according to claim 3, wherein the antibodies are selected from monoclonal antibodies, polyclonal antibodies or mixtures of monoclonal antibodies.

5. The isolated binding member according to claim 1, wherein the binding member is monospecific towards the PsaA protein.

6. The isolated binding member according to claim 1, wherein the binding member is bispecific having at least one portion specific towards the PsaA protein.

7. The isolated binding member according to claim 1, wherein the binding member is multispecific having at least one portion towards the PsaA protein.

8. The isolated binding member according to claim 1, wherein the binding domain is carried by a human antibody framework.

9. The isolated binding member according to claim 1, wherein the binding domain is carried by a humanised antibody framework.

10. The isolated binding member according to any of the preceding claims, wherein said binding domain recognizes an epitope in the N-terminal part of PsaA.

11. The isolated binding member according to any of the preceding claims, wherein said binding domain recognizes an epitope in the N-terminal 100 amino acid residues of PsaA.

12. The isolated binding member according to any of the preceding claims, wherein the binding domain comprises an amino acid sequence selected from SEQ ID NO 2, from SEQ ID NO 4, from SEQ ID NO 6, and from SEQ ID NO 8 or a homologue thereof.

13. The isolated binding member according to claim 12, wherein the binding domain comprises at least two amino acid sequences selected from SEQ ID NO 2, from SEQ ID NO 4, from SEQ ID NO 6, and from SEQ ID NO 8 or a homologue thereof.

14. The isolated binding member according to claim 12, wherein the binding domain comprises at least SEQ ID NO 4, and SEQ ID NO 6, or a homologue thereof.

15. The isolated binding member according to claim 12, wherein the binding domain comprises SEQ ID NO 2, SEQ ID NO 4, and SEQ ID NO 6, or a homologue thereof.

16. The isolated binding member according to claim 12, wherein the binding domain comprises SEQ ID NO 8, or a homologue thereof.

17. The isolated binding member according to any of the preceding claims, wherein the binding member is capable of binding PsaA from two or more different Pneumococcus serotypes.

18. The isolated binding member according to any one of claims 12-17, wherein the homologue is at least 60 % homologous to one or more of the sequences selected from SEQ ID NO 2, from SEQ ID NO 4, from SEQ ID NO 6, and from SEQ ID NO 8, such as at least 65 % homologous such as at least 70 % homologous, such as at least 75 % homologous, such as at least 80 % homologous, such as at least 85 % homologous, such as at least 90 % homologous, such as at least 95 % homologous, such as at least 98 % homologous.

19. The isolated binding member according to any of the preceding claims, wherein said binding member is capable of binding to an epitope on PsaA, said epitope being recognized by the binding member as defined in any one of claims 12-16.

20. The isolated binding member according to any of the preceding claims, wherein the binding domain is located in a V_L domain.

21. The isolated binding member according to any of the preceding claims, wherein the binding domain is located in a V_H domain.

22. The isolated binding member according to any one of claims 12-15, wherein the binding domain is arranged as a complementarity-determining region (CDR) in the binding member.

23. The isolated binding member according to claim 3, wherein the fragment of antibodies are selected from Fab, Fab', $F(ab)_2$ and Fv.

24. The binding member according to any of the preceding claims, comprising at least a first binding domain and a second binding domain, said first binding domain being capable of specifically binding Streptococcus pneumoniae surface adhesin A (PsaA) protein, and said second binding domain is different from said first binding domain.

25. The isolated binding member according to claim 24, wherein the second binding domain is capable of specifically binding a mammalian protein, such as a human protein, such as a protein selected from CD64 or CD89.

26. The isolated binding member according to claim 24, wherein the second binding domain is capable of specifically binding a mammalian cell, such as a human cell, such as a cell selected from a leucocyte, macrophages, lymphocytes, neutrophilic cells, basophilic cells, and eosinophilic cells.

27. The isolated binding member according to claim 24, wherein the second binding domain is capable of specifically binding a Pneumococcus protein.

28. The isolated binding member according to claim 27, wherein second binding domain is capable of specifically binding a PsaA epitope different from the first binding domain.

29. The isolated binding member according to claim 24, wherein the binding member comprises two binding domains.

30. The isolated binding member according to claim 29, wherein the two binding members are linked through a spacer region.

31. An isolated nucleic acid molecule encoding at least a part of the binding member as defined in any one of claims 1-30.

32. A vector comprising the nucleic acid molecule as defined in claim 31.

33. The vector according to claim 32, comprising a nucleotide sequence which regulates the expression of the antibody encoded by the nucleic acid molecule.

34. A host cell comprising the nucleic acid molecule as defined in claim 31.

35. A cell line engineered to express the binding member as defined in any of claims 1-30.

36. A method of detecting of diagnosing a disease or disorder associated with Pneumococcus in an individual comprising

- providing a biological sample from said individual,
- adding at least one binding member as defined in any of claims 1-30 to said biological sample,
- detecting binding members bound to said biological sample, thereby detecting or diagnosing the disease or disorder.

37. A kit comprising at least one binding member as defined in any of claims 1-30, said antibody being labelled.

38. A pharmaceutical composition comprising at least one binding member as defined in any of claims 1-31.

39. The pharmaceutical composition according to claim 38, comprising at least two different binding members.

40. Use of a binding member as defined in any of claims 1-30 for the production of a pharmaceutical composition.

41. Use of a binding member as defined in any of claims 1-30 for the production of a pharmaceutical composition for the treatment of Pneumococcus infection.